REMARKS

Claims 159, 161, 162, 163, 170 to 178, 180 to 191, 193, 194, 195, 198 to 202, 222 to 255 are pending in the application. Claims 177, 178, 181, 182, 183, 184, 185, 186, 190, 191, and 195 have been withdrawn from consideration.

No new matter has been added by the amendments submitted herein, as explained further below.

Applicants note that office action summary indicates that claims 195 to 227 are withdrawn from consideration, but that these claims were examined on the merits.

Applicants submitted an Information Disclosure Statement on March 20, 2003. Receipt of this is not acknowledged in the action of April 8, 2003. Enclosed is a copy of Applicants' receipt card, stamped the PTO, indicating a receipt date of March 20, 2003. This material is being re-submitted by Applicants, separately, in view of the large number of pages of material.

Elements of claims 159 and 160 have been combined to obtain amended claim 159. Claim 160 has been cancelled.

Dependent claims 228 to 255 are new in the application. Elements introduced by these claims are based on the application as filed, as follows:

Claim	Basis
228, 233, 237, 241, 245, 249, 253	Claim 163

Claim	Basis
229, 234, 238, 242, 246, 250, 254	Claim 216
230, 235, 239, 243, 247, 251, 255	Claim 219
231	Page 27, line 3 of last paragraph
232, 240	Page 24, paragraph 8
236	Page 23, line 2, and claim 161
244	Page 28, paragraph 5
248	Page 11, third paragraph from the bottom
252	Page 27, last line

Claim 159 has been amended to incorporate limitations of former claim 160. Claim 160, now cancelled, was rejected for being obvious in view of the teachings of Diamond *et al.* in combination with Julius *et al.* Applicants respectfully submit that there is no motivation provided by the art of record to combine any teachings of Diamond *et al.* and Julius *et al.*

In providing the backdrop against which the results of their research are presented, Diamond *et al.* state, "[a] widespread mechanism of host defense in the animal kingdom is the production of antibiotic peptides." (Second paragraph of text in first column of page 5156) Diamond *et al.* go on to state, "[f]actors that govern the regulated

Received from < 416 865 7380 > at 9/8/03 12:27:33 PM [Eastern Daylight Time]

expression of mammalian antibiotic peptides are *poorly* understood." (Emphasis added, second paragraph, in second column of page 5156) "Based on the up-regulation of genes encoding antimicrobial peptide and proteins previously observed for insect epithelial cells responding to bacterial components, we sought evidence for an analogous host defense response in mammalian airway cells. ... The bacterial membrane component lipoplysaccharide (LPS) was found to be a potent stimulus for the epithelial cell response. The mechanism by which the TECs recognize LPS was also addressed in these studies." (Second paragraph, in second column of page 5156)

In short, Diamond *et al.* set out to study the mechanism(s) by which tracheal antimicrobial peptides (TAPs) are expressed by epithelial cells when induced by LPS. To this end, Diamond *et al.* established that TAP mRNA levels in bovine TECs increased in response to exposure to LPS in a concentration-dependent manner. (first paragraph of Results and Discussion on page 5157)

Diamond *et al.* were aware of the existence of CD14, in both its membrane-bound and soluble forms, and that CD14 can act as a receptor for LPS: "CD14 molecule is a major mammalian receptor for LPS, although other candidate receptors have been identified. CD14 exists in two forms, a glycosl phosphatidylinositol-anchored membrane form characterized from macrophages and a soluble form. The soluble form, found in serum, can mediate LPS-stimulated responses in endothelial and epithelial cells." (Paragraph bridging pages 5157 and 5158)

In fact, Diamond *et al.* observed serum-augmented TAP expression, but concluded, in view of other observations, that induction of TAP does *not* involve serum-derived CD14: "In our studies, we found that serum augments a response of TECs to LPS. However, in all other experiments, the cell preparation and culture conditions contained no serum. This suggested that the observed TAP does not involve serum-derived CD14." (Paragraph bridging pages 5157 and 5158)

Diamond *et al.* thus conducted experiments to determine the source of CD14 involved in the expression of TAP, and found it to be endogenously produced: "We therefore tested if the cultured cells might serve as a potential endogenous source of CD14. ... CD14 mRNA was found in all samples, including cultured TECs (Fig. 2) consistent with expression of CD14 in each of these sources. (Paragraph bridging pages 5157 and 5158)

Diamond *et al.* thus teach that induction of TAP expression in the presence of LPS requires the production of endogenous CD14, which because their results indicated was *not* soluble CD14, would be membrane-bound CD14.

Diamond *et al.* thus went on to test this explanation of their results by adding anti-CD14 antibody, to find that the antibody "My4 blocked the LPS-stimulated increase in TAP mRNA levels in a concentration-dependent manner." (Paragraph bridging pages 5157 and 5158)

Diamond *et al.* thus teach that LPS-induced TAP production by TECs involves an LPS-CD14 (membrane-bound form) interaction. There is no suggestion that addition of exogenous CD14 would induce TAP or other defensin production.

Julius *et al.* teach activation of B cells by CD14. There is no suggestion that exposure of epithelial cells will result in the production of a defensin.

Applicants thus respectfully submit that the invention defined by the claims as amended, which claims require stimulating or enhancing expression of at least one defensin by directly exposing epithelial cells or epidermis to soluble CD14 (or equivalent), is neither taught, nor suggested by the teachings of Diamond *et al.*, alone or in combination with Julius *et al.*, or any other prior art of record.

Received from < 416 865 7380 > at 9/8/03 12:27:33 PM [Eastern Daylight Time]

Applicants believe that all of the issues addressed in the outstanding Action have been addressed in this response, and thus request allowance of the application.

Note Regarding Representation

The undersigned, an appointed agent of the Applicants, has recently changed firms. The new address and telephone number of the undersigned are indicated below. A change of address of the undersigned is on record with the PTO.

In the event that any issues remain, the Examiner is invited to telephone the undersigned at (416) 865-8281 with any proposal to advance prosecution.

Yours very truly,

September 8, 2003
Date

John C. Hunt
Registration No. 36,424

Torys LLP
Suite 3000
79 Wellington Street West
Box 270, TD Centre
Toronto, Ontario
M5L 1A9
Canada

Received from < 416 865 7380 > at 9/8/03 12:27:33 PM [Eastern Daylight Time]